

Friedreich's ataxia induced pluripotent stem cells model intergenerational GAATTC triplet repeat instability.

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Authors:	Sherman Ku, Elisabetta Soragni, Erica Campau, Elizabeth A Thomas, Gulsah Altun, Louise C Laurent, Jeanne F Loring, Marek Napierala, Joel M Gottesfeld
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Public Summary:

Using reprogramming technology, skin cells from individuals with genetic disease can be turned into self-renewing pluripotent stem cells (induced pluripotent stem cells; iPSCs). We are using iPSCs in research to understand the the inherited neurodegenerative disease Friedreich's ataxia (FRDA). FRDA is one of a group of diseases called "triplet repeat" diseases, because they are caused by expansion of a sequence of three DNA "letters". In the case of FRDA, the repeated triplet is GAA. Normally there are a few repeats (<30) of this sequence in a gene called frataxin; the repeats are not in the part of the gene that codes for the protein; instead they are in an "intron". Introns are normal parts of genes in the DNA that are removed when the DNA is copied to make RNA, which guides the production of the protein. In people with the disease, there are more than 100 copies of GAA inside one of the introns; this causes the DNA around the repeats to be inactivated, which shuts down the fraxin gene. The fraxin gene is necessary for proper connections to be made between nerve cells. If there is not enough fraxin protein, nerves start to degenerate, causing weakness and lack of balance. The pathological expansion of the GAA sequence occurs between generations during development of germ cells. Individuals with a normal number of GAA repeats can have children with greatly expanded numbers of repeats, resulting in the disease. We found that when we took skin cells from people who already had large expansions, the region expanded even more when the cells were reprogrammed. This is the first time that anyone has seen a dramatic change like this occur as a result of reprogramming cells. We think that the same molecular process that causes the intergenerational expansion also causes the expansion caused by reprogramming. This is a true example of a "disease in a dish", in which we can study the causes of a disease as it happens.

Scientific Abstract:

The inherited neurodegenerative disease Friedreich's ataxia (FRDA) is caused by GAATTC triplet repeat hyperexpansions within the first intron of the FXN gene, encoding the mitochondrial protein frataxin. Long GAATTC repeats cause heterochromatin-mediated gene silencing and loss of frataxin in affected individuals. We report the derivation of induced pluripotent stem cells (iPSCs) from FRDA patient fibroblasts by transcription factor reprogramming. FXN gene repression is maintained in the iPSCs, as are the global gene expression signatures reflecting the human disease. GAATTC repeats uniquely in FXN in the iPSCs exhibit repeat instability similar to patient families, where they expand and/or contract with discrete changes in length between generations. The mismatch repair enzyme MSH2, implicated in repeat instability in other triplet repeat diseases, is highly expressed in pluripotent cells and occupies FXN intron 1, and shRNA silencing of MSH2 impedes repeat expansion, providing a possible molecular explanation for repeat expansion in FRDA.

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